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EXAMINER	
MYERS, CARLA J	
ART UNIT	**PAPER NUMBER**
1634	

NOTIFICATION DATE	DELIVERY MODE
05/16/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/695,744	PATERLINI-BRECHOT, PATRIZIA	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 4, 5, 9-18 and 20-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5,9-18 and 20-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 28, 2007 has been entered.

Applicant's arguments and amendments set forth in the response of March 28, 2007 have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

2. Claims 1, 4, 5, 9-18, and 20-25 are pending and have been examined herein.

Maintained Rejections

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 5, 9-12, and 20-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kalionis in view of Vona (American Journal of Pathology. January 2000. 156: 57-63; cited in the IDS).

Kalionis teaches a method for prenatal diagnosis of fetal cells isolated from maternal blood. The reference (page 3) states that "(t)he present invention is directed to a method for easily enriching and identifying trophoblast cells in maternal peripheral blood in the presence of a population of blood cell types. The enrichment, identification and analysis of trophoblast cells in peripheral blood provides a means by which non-invasive prenatal diagnosis can be carried out. This method is therefore of particular value in prenatal testing to obtain genetic and/or biochemical information about the fetus."

The method of Kalionis (pages 5-7) comprises the steps of:

a) diluting a sample of maternal blood in a solution comprising a reagent for lysing red blood cells;

b) filtering the diluted sample of maternal blood through a filter according to size, in order to separate fetal cells from maternal blood cells;

c) analyzing the cells retained on the filter by immunostaining for trophoblast-specific markers, in order to confirm the identify of the cells as being of fetal origin (see also page 8);

d) analyzing individual cells by in situ hybridization and immunostaining to demonstrate that the cells are fetal cells (see also pages 10 and 18); and

e) analyzing the individual fetal cells to detect a genetic anomaly or to determine the sex of the fetal cells (see also pages 9-10 and page 21).

With respect to step a) of the present invention, Kalionis (page 7) teaches that prior to filtration, the maternal blood may be diluted and treated by a variety of

techniques that will lead to the lysis of erythrocytes (red blood cells). In particular, Kalionis teaches that dilution of the blood sample in a hypotonic buffer results in the lysis of erythrocytes (red blood cells), thereby reducing the number of cells needed to be filtered and reducing the incidence of coagulation. Accordingly, Kalionis teaches the step of diluting a sample of maternal blood in a filtration solution comprising a reagent for lysing red blood cells.

Kalionis does not teach collecting the individual fetal cells retained on the filter by microdissection, wherein the microdissection uses a laser to recover single collected cells in a tube.

However, Vona teaches methods for isolating rare cells from blood wherein the methods comprise passing a blood sample through a filter to retain target cells according to size, analyzing the cells retained on the filter to confirm their identity, using microdissection with the aid of a laser to individually collect the isolated cells retained on the filter into a tube in order to obtain a single collected cell (see pages 58-60). Vona (page 60) teaches that the isolated cells are then lysed and preamplified by PCR prior to genetic analysis using less than one fifth (i.e., 5 out of 60 ul) of the preamplified DNA preparation. It is stated that the use of microdissection to isolate individual cells, followed by the amplified of DNA from the individual cells provides the advantage of a highly sensitive technique for detecting genetic abnormalities (page 58). It is also stated that the method of isolating cells by filtration followed by amplification of the nucleic acids in the isolated cells provided improved results over methods which relied on PCR alone (pages 58 and 62). The method is characterized as being "easy to perform, rapid,

and inexpensive" (page 61). The method also provides the advantage of allowing for the isolation of individual cells without damaging the morphology of the cells, thereby providing increased sensitivity (page 61). Additionally, Vona (page 62) states that the method "allows the isolation of large, circulating, nontumorous cells. For example, the isolation of trophoblastic cells from the peripheral blood of pregnant women has been initiated in our laboratory and may constitute an important step toward improving the prenatal diagnosis of genetic diseases."

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kalionis so as to have individually collected the fetal cells retained on the filter by laser microdissection as disclosed by Vona in order to have provided an efficient and effective means for isolating the individual fetal cells that would allow for the confirmation of the identity of the individual cells and the genetic analysis of the individual cells. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have preamplified the genetic material obtained from the isolated cells in order to have achieved the benefit set forth by Vona of increasing the sensitivity of detection of genetic anomalies in the isolated cells.

With respect to step a) of the present invention, Kalionis (page 7) teaches that prior to filtration, the maternal blood may be diluted and treated by a variety of techniques that will lead to the lysis of erythrocytes (red blood cells). In particular, Kalionis teaches that dilution of the blood sample in a hypotonic buffer results in the lysis of erythrocytes (red blood cells), thereby reducing the number of cells needed to

be filtered and reducing the incidence of coagulation. Accordingly, Kalionis teaches the step of diluting a sample of maternal blood in a filtration solution comprising a reagent for lysing red blood cells.

Furthermore, Vona teaches that prior to filtration, the blood sample is diluted 1:10 in a solution containing saponin (an agent for lysing red blood cells) and paraformaldehyde (a reagent for fixing nucleated cells). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kalionis so as to have diluted the maternal blood in a buffer that contained both an agent for fixing nucleated cells and an agent for lysing red blood cells in order to have provided an effective means for preparing the blood sample for filtration and for further analysis of nucleated cells present in the blood sample.

With respect to claims 4 and 5, in the method of Vona, the cells retained on the filter are collected individually by microdissection, wherein microdissection consists of laser cutting a portion of the filter on which the cells are retained and recovering a single collected cell in a suitable tube (pages 58-60).

With respect to claims 9 and 11, modification of the method of Kalionis to collect the cells on the filter by microdissection and to preamplify the nucleic acids present in the collected cells prior to analysis would have resulted in a method of identifying one or more genetic targets, and particularly a genetic or chromosomal anomaly, in the preamplification product.

Regarding claims 10 and 12, in the method of Vona, the amplification is performed using less than one fifth of the preamplification product (i.e., (i.e., 5 out of 60 ul, see page 60).

With respect to claim 20, the reference teaches that the maternal blood samples are obtained form women at 30-37 weeks of pregnancy (see Table 1).

With respect to claim 21, the reference (page 7) teaches obtaining and filtering 5-100 ml of maternal blood. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have practiced the method of Kalionis in view of Vona using a sample of about 5ml and then further diluting the sample since this constitutes an acceptable quantity of maternal blood to obtain from a pregnant woman in order to allow for the analysis of fetal cells present in the maternal blood.

With respect to claim 22, Kalionis teaches that the blood can be diluted with an isotonic buffer to reduce the viscosity prior to filtering or in a hypotonic buffer to lyse red blood cells and thereby reduce the number of cells that need to be filtered and the incidence of coagulation. Kalionis does not specifically exemplify methods in which the blood is diluted 10 to 100 fold. However, Vona (page 58) teaches collecting 6 ml of blood and diluting the blood 1:10 in filtration solution prior to filtering. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kalionis so as to have diluted the blood 1:10 fold in the filtration solution prior to filtering in order to have reduced the viscosity of the

blood and thereby to have optimized the filtration process and the isolation of individual fetal cells for prenatal diagnosis.

With respect to claims 23-25, Kalionis does not teach filtering the blood sample through a polycarbonate membrane with a pore density is in the range of "5 X 10^4 to 5 X 10^5 pores/m^2" (or 5 X 10^4 to 5 X 10^5 pores/cm^2) and does not specifically teach pore sizes of 8 um. However, regarding claim 23, Kalionis does teaches that the filter has a pore size of 10 um (page 4), which is considered to meet the limitation in the claim of "about 8 um." Further, Vona (page 58) teaches that the blood samples are filtered through a polycarbonate filter calibrated with 8um cylindrical pores. Vona also teaches that each sample is filtered through a 0.6-cm diameter circular spot on the filter and that the cells were laser cut from the filter for collection. To have determined the optimum density of the pores that would have allowed for the isolation and collection of individual fetal cells would have been obvious to one of ordinary skill in the art and well within the skill of the art. As discussed in MPEP2144.05(b), "(w)here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller,* 220 F.2d 454, 105 USPQ 233, 235 (CCPA 1955). In particular, Vona teaches the criticality of selecting an appropriate filter wherein the filter and pore sizes are sufficient to retain the cell of interest and wherein the pores are spaced sufficiently a part to allow for the separation and collection of individual cells. Accordingly, the selection of a polycarbonate filter having an optimum pore density, including a pore density of 5 X 10^4 to 5 X 10^5 pores/cm^2 , would have been obvious to one of ordinary skill in the art and well within the skill of the

art at the time the invention was made in order to have to have accomplished the objective of isolating and collecting the single fetal cells, thereby facilitating the method of prenatal diagnosis.

4. Claims 13, 14, 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kalionis in view of Vona (2000) and further in view of Bianchi (U.S. Patent No. 5,614,628; cited in the IDS) .

The teachings of Kalionis and Vona are presented above.

With respect to claim 13, the combined references do not teach sequencing the amplified fetal DNA. However, Bianchi (paragraph 31) teaches sequencing amplified fetal DNA in order to detect the presence of genetic variation in the fetal DNA and teaches that sequencing may be used in place of or in addition to detection of genetic variations by PCR or hybridization analysis. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kalionis so as to have sequenced the amplified fetal DNA in order to have achieved the benefit of providing a sensitive and effective means for detecting genetic variation in the fetal DNA thereby facilitating the method of prenatal diagnosis.

With respect to claim 14, the combined references do not teach using a probe to analyze the amplified DNA. However, Bianchi (e.g., paragraph 31) teaches that PCR amplified DNA can be analyzed by probe hybridization to detect nucleic acid sequence variations. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kalionis so as to have detected the amplified fetal DNA by probe hybridization in order to have achieved the

benefit of providing a sensitive and effective means for detecting genetic variation in the fetal DNA, thereby facilitating the method of prenatal diagnosis.

With respect to claim 16, Kalionis does not specifically teach detecting at least one polymorphism, such a SNP. However, Bianchi teaches methods of prenatal diagnosis which include the detection of polymorphisms, such as that associated with sickle cell anemia (see paragraph 46) and paternally inherited polymorphisms (paragraph 35). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kalionis so as to have specifically detected a polymorphism associated with sickle cell anemia in order to have allowed for the prenatal diagnosis of sickle cell anemia or to have specifically detected the paternally inherited polymorphism disclosed by Bianchi in order to have confirmed the identity of female fetal cells and to have distinguished female fetal cells from maternal cells.

With respect to claim 17, the combined references do not teach analyzing the fetal nucleic acids in order to demonstrate the biparental contribution of fetal DNA.

However, Bianchi teaches methods of prenatal diagnosis wherein the methods are carried out using nucleic acid probes that detect nucleic acids that are specific for both maternally and paternally derived nucleic acid sequences (see, e.g., paragraph 35 and 104-106). In view of the teachings of Bianchi, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kalionis so as to have analyzed the fetal nucleic acids for markers specific for each parent in order to have provided a method that would have allowed one to distinguish

between female fetal DNA and maternal DNA, thereby confirming the identity of the fetal cells and which would have allowed for the identification of both paternally and maternally inherited sequences in the fetal cells.

5. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kalionis in view of Vona (2000) and Fodor (U.S. Patent No. 6,309,822) .

The teachings of Kalionis and Vona are presented above. The combined references do not teach detecting a genetic anomaly or genotype using DNA probes fixed to a microarray.

However, Fodor teaches methods for detecting mutations and polymorphisms using microarrays wherein a nucleic acid probe comprising a mutation/polymorphism or a wildtype sequence is immobilized onto an array and the array is contacted with a sample nucleic acid (see, e.g., paragraphs 714-716). Fodor (paragraph 368) states that microarrays can be used to simultaneously analyze multiple samples for a large number of genetic markers and allows for simplified, economized and more generally accessible prenatal screening.

In view of the teachings of Fodor, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kalionis so as to have detected the genetic mutations or polymorphisms using a microarray in order to have obtained the advantages set forth by Fodor of providing a method which allowed for the simultaneous analysis of multiple samples and the detection of a plurality of mutations or polymorphisms, thereby providing a faster, more efficient and economical method of prenatal diagnosis.

6. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kalionis in view of Vona (2000), and further in view of Pinkel (U.S. Patent No. 6159685).

The teachings of Kalionis and Vona are presented above. In particular, Kalionis teaches prenatal diagnosis of fetal cells by in situ hybridization but does not teach using comparative genomic hybridization (CGH) for prenatal diagnosis.

However, Pinkel (paragraph 41) teaches the method of comparative genomic hybridization and teaches the application of this method to prenatal diagnosis by assaying nucleic acid sequences of fetal cells (see, e.g., paragraphs 8 and 14). Specifically, Pinkel (paragraphs 14 and 41) teaches that CGH employs the methodology of in situ hybridization in order to detect extra or missing copies of whole chromosomes or parts of chromosomes. Pinkel (paragraph 14) states: "(w)hen CGH is applied, for example, in the fields of tumor cytogenetics and prenatal diagnosis, it provides methods to determine whether there are abnormal copy numbers of nucleic acid sequences anywhere in the genome of a subject tumor cell or fetal cell or the genomes from representative cells from a tumor cell population or from a number of fetal cells, without having to prepare condensed chromosome spreads from those cells. Thus, cytogenetic abnormalities involving abnormal copy numbers of nucleic acid sequences, specifically amplifications and/or deletions, can be found by the methods of this invention in the format of an immediate overview of an entire genome or portions thereof. More specifically, CGH provides methods to compare and map the frequency of nucleic acid sequences from one or more subject genomes or portions thereof in relation to a reference genome. It permits the determination of the relative number of copies of

nucleic acid sequences in one or more subject genomes (for example, those of tumor cells) as a function of the location of those sequences in a reference genome (for example, that of a normal human cell)."

In view of the teachings of Pinkel, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kalionis so as to have analyzed the isolated fetal cells by CGH in order to have provided a rapid and effective means for identifying genetic anomalies in the fetal nucleic acid, thereby facilitating the method of prenatal diagnosis.

RESPONSE TO ARGUMENTS

7. In the response of March 28, 2007, Applicants traversed each of the above rejections for the reasons set forth in the previous reply of November 28, 2006. Accordingly, the response to Applicants previous arguments set forth in the Office actions of June 26, 2006 and December 20, 2006 apply equally to the present grounds of rejection.

Further, in the response of March 28, 2007, Applicants make the general statement that there must be a reasonable expectation of success at combining references and there must be a motivation to combine references. Given the extensive guidance provided by Vona of how to practice such the ISET method, it is maintained that the ordinary artisan would have had a reasonable expectation of success of modifying the method of Kalionis so as to have isolated the cells retained on the filter by microdissection and to have analyzed the nucleic acids of the microdissected cells by amplification procedures Further, Vona specifically provides the motivation to apply the ISET methodology to the analysis of nucleic acids obtained from cells present in

maternal blood (i.e., to combine the teachings of Vona with Kalionis). In particular, Vona states that "(t)he potential uses for ISET go well beyond the field of oncology, because it also allows the isolation of large, circulating, nontumorous cells. For example, the isolation of trophoblastic cells from the peripheral blood of pregnant women has been initiated in our laboratory and may constitute an important step toward improving the prenatal diagnosis of genetic diseases." It is noted that obviousness does not require absolute predictability but only the reasonable expectation of success. See In re Merck and Company Inc., 800 F. 2d 1091, 231 USPQ 375 (Fed. Cir. 1986) and In re O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988). In the present situation, the teachings of Vona provide both the motivation to combine teachings and a reasonable expectation of success. Further, Applicant's response does not provide any specific arguments as to why the method of Vona is not enabling. That is, there are no specific arguments provided as to why one of ordinary skill in the art, apprised of the ISET methodology and the teachings of Vona to use this methodology to isolate trophoblast cells from pregnant women and use the resulting isolated cells for prenatal diagnosis, would not be able to successfully practice such a methodology.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach

the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)-272-0735.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866)-217-9197 (toll-free).

Carla Myers
Art Unit 1634